REMARKS

Claims 1-8 and 12-14 are pending. Claim 1 has been amended to reflect that 1) the diffusion-controlled membrane embodiments of the invention encompass a single membrane layer; 2) that, as noted by the Examiner, one feature of the matrix embodiments of the present invention is that a single lipid/fat/wax component may be used in the matrix; and 3) that the instant formulations are intended for ingestion. Claim 12 has been amended also to recite the "ingestion" language and to add standard language for method claims. No new matter has been introduced by the amendments to the claims.

Claims 1, 2, 5, 6 and 12-14 have been rejected for allegedly being unpatentable under 35 U.S.C. §103(a) in view of U.S. Patent 5,462,749 to Rencher ("Rencher"). The Examiner asserts that Rencher teaches the use of xanthan gum to "retard release" of actives, including cholesterol-lowering agents.

In the first place, Applicants reiterate something the Examiner apparently has not appreciated: Rencher uses xanthan gum in combination with sodium carboxymethylcellulose to confer bioadhesive properties to the formulations; one of skill in the art would recognize this. Furthermore, even if Rencher is concerned with sustained release, it is certainly not at all in connection with formulations to be ingested.

Rencher is directed to drug-release formulations applied to the site of action, not those which are swallowed (ingested) so as to allow drug absorption via the gastrointestinal tract of a patient. Support for this assertion is found in Rencher, col. 4,

lines 22- 28 where it is disclosed that the preferred dosage forms are "administered orally, nasally, rectally, vaginally, ophthalmically, optically, or topically." It is apparent from col. 4, lines 26-28, that the intended meaning of "orally" as used in line 23 refers to the topical application of the bioadhesive gel of Rencher to the site of action in the mouth. The totality of the teaching of Rencher is directed to bioadhesive pharmaceutical carriers which release a pharmaceutical at the site of action and the problems solved thereby in the treatment of moist membranes of the body. (See col. 1, lines 17-30 and 49-53.)

In contrast, the present invention is directed to controlled-release pharmaceutical preparations of fluvastatin which are ingested, so that fluvastatin is absorbed by the gastrointestinal tract into the bloodstream, and, like other HMG-CoA reductase inhibitors, acts in the liver to reduce the level of circulating LDL cholesterol. The bioadhesive quality of the formulations of Rencher which makes the drug carried therein remain at a moist area of application, such as the mouth, is contradictory to the purpose of obtaining a controlled-release ingested formulation of a drug.

Further, while, as the Examiner correctly asserts, Rencher cites, at col 3., line 44, cholesterol-lowering agents as one drug class which can be included in the bioadhesive dosage form, no support is found in Rencher for a controlled-release ingested formulation of any cholesterol-lowering agent. Moreover, since the stated object of Rencher is to provide bioadhesive drug

formulations applied to the site of action, the inclusion of cholesterol-lowering agents among the diverse list of pharmaceutical actives which can be included in the bioadhesive dosage form is unsupported, since, as stated, the site of action of fluvastatin and all HMG-CoA reductase inhibitors is in the liver, an internal organ.

Thus, the "controlled release" of the Rencher semisolid or solid, topical formulation and such release with respect to the ingested instant formulations are not at all the same. The issue raised by the Examiner of the Rencher recitation of the "highly soluble drug" boric acid as an active is thus not of relevance to the consideration of patentability of the instant invention. Applicants note further that the ingestion of boric acid, the Rencher active cited by the Examiner, is, to say the least, contraindicated. Applicants have argued, rightly, that they have addressed the problem, ignored by Rencher (and the other cited prior art), of delivering by ingestion a highly soluble substance in a sustained-release vehicle.

Applicants note still further that the Rencher examples have benzocaine as the active ingredient; the Rencher definition of what constitutes a "highly water soluble drug" is not that understood in the field. Benzocaine has an aqueous solubility of 1g/2500ml (Merck Index, 11th Ed., p.1114, copy enclosed); fluvastatin has a solubility of more than 50g/1000ml (instant specification, p. 5, ll. 7 and 8). The instant specification defines "water soluble" as a solubility of more than 30g/1000ml at body temperature (p.7, ll. 6 and 7).

For all the reasons set forth above, the present invention is not obvious in view of Rencher.

Claims 1-4, and 12-14 have again been rejected under 35 U.S.C §103(a) for allegedly being unpatentable over U.S. 5,576,016 to Amselem *et al.* ("Amselem") or U.S. Patent 5,023,089 to Sakamoto *et al.* ("Sakamoto"). The Examiner asserts that it would have been obvious to one skilled in the art to deliver the fluvastatin of the instant invention using the vehicle of Amselem or Sakamoto. However, although, as cited by the Examiner, the vehicle of Amselem may comprise a constituent (a wax) in common with the instant vehicle, the former vehicle is an entirely different drug delivery formulation than that of the present invention.

Amselem teaches a pharmaceutical composition comprising nanoemulsions of particles comprising a lipid core, composed of lipid, which may be a wax, stabilized by at least one phospholipid envelope. (See col. 2, lines 29 - 33). The compositions of Amselem have features intermediate between liposomes and oil-in-water emulsions. In contrast, the present invention is *not* a nanoemulsion as described in Amselem, but a solid matrix. Matrix formulations according to the ordinary meaning in the art are those comprised of aggregated mixtures of granulate constituents optionally compressed together.

Further, the stabilizing phospholipid envelope(s) is an essential feature of the Amselem formulations; the present invention does not include such a feature. Therefore, the

vehicle of Amselem and the matrix of the present invention are entirely different drug delivery systems.

Sakamoto teaches sustained-release preparations for water-soluble pharmaceuticals comprising two or more fats having different melting points wherein manufacture of the preparation comprises a first step of maintaining the temperature of the mixture or suspension of components above the melting point of the fat with a higher melting point, followed by spray cooling to form granules, and then an annealing step at a temperature between that of the lower-melting-point fat and the higher-melting-point fat. (See col. 1, lines 40-59.) The formulation of Sakamoto is not a matrix according to the ordinary meaning in the art.

The present invention as claimed in claims 1-8 and 12-14 relates to matrix formulations and diffusion-controlled membrane formulations of fluvastatin. Advantageously, the matrix formulation of the present invention may employ only one matrix material. Claims 4 and 6 of the subject application, as amended in the Amendment and Response filed November 17, 1999, uses Markush group language to embody this feature with respect to specific compounds. In claim 4, for example, "the matrix material is selected from the group consisting of polyethylene oxide, hydroxypropyl methyl cellulose and paraffin." Further of advantage, preparation of the formulations of the present invention does not require any melting or spray cooling technique.

The formulations according to Amselem and Sakamoto are not matrix formulations according the ordinary meaning in the field, i.e., the meaning conveyed in the instant specification and claims. Matrix formulations according to the ordinary meaning are those comprised of aggregated mixtures of granulate constituents optionally compressed together.

Claims 1, 2, 7, 8, and 12-14 have been rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over U.S. 5,395,626 to Kotwal *et al.* ("Kotwal") or U.S. 5,238,686 to Eichel *et al.* ("Eichel"). Again, it is the Examiner's opinion that it would be obvious to deliver the fluvastatin of the instant invention using the vehicle of Kotwal or Eichel.

Kotwal discloses a multi-layered, controlled-release pharmaceutical dosage form consisting of a drug-containing core and at least one other drug-containing layer, each surrounded by a controlled-release layer. Eichel discloses a dual-wall, coated dosage form for a water-soluble drug having an inner-wall microencapsular control coating and an outer-wall enteric coating (See col. 3, lines 22-25.) As the Examiner has noted, the diffusion-controlled membrane formulations of the present invention can have a single membrane layer (a single coat). Applicants have amended claim 1 of the subject application herein to reflect this limitation.

Applicants have found, unexpectedly, that fluvastatin, a highly water-soluble drug by any accepted definition of the term in the art, is, despite its high solubility, released over a prolonged period of time when formulated according to the instant

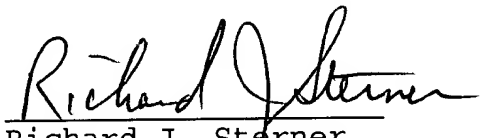
invention and subjected to conditions enhancing drug release. Even more unexpectedly, the release of fluvastatin was slower than that of tested drugs with lower water solubility. Nothing in the cited prior art provides any expectation or suggestion of these observed phenomena.

As set forth above, the instantly claimed subject matter is patentably distinct from the disclosure of the cited references. Furthermore, the amendments herein to the claims have put them into proper form for allowance. No new matter has been introduced nor have any new issues been raised by said amendments. Reconsideration and allowance of pending claims 1-8 and 12-14 are respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fee which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: September 6, 2000

Respectfully submitted,



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Enclosure